Recent Advances in Nickel Catalysis Enabled by Stoichiometric Metallic Reducing Agents

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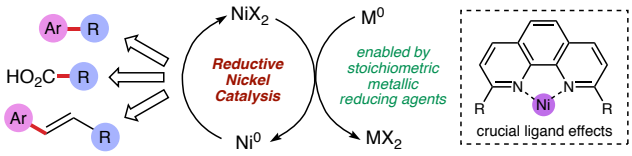


Received:
Accepted:
Published online:
DOI:

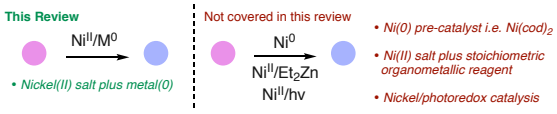
Abstract This short review describes recent advances in the field of nickel-catalysis, specifically transformations employing stable Ni(II)-pre-catalysts that are activated *in situ* with the use of stoichiometric metallic reducing agents. The article seeks to summarise the field, highlighting key studies and discussing mechanistic facets. The review closes with one eye on future directions in redox-enabled nickel catalysis.

Key words nickel catalysis, reductive cross-coupling, reductive carboxylation, organometallic, ligand-effects, ligand-induced selectivity.

1. Introduction

Transition metal catalysed reactions are amongst the most reliable and commonly used transformations in the organic chemist's toolkit. The importance of palladium catalysed cross-coupling reactions was recognised with the award of the 2010 Nobel Prize for chemistry.[1] Despite palladium's standing as the premier amongst transition metals, nickel has long found application in organometallic chemistry with Sabatier awarded the 1912 Nobel Prize in Chemistry for the nickel-mediated hydrogenation of ethylene.[2] In the intervening century, interest in the catalytic properties of nickel complexes has ebbed and flowed, however over the past decade, researchers have truly begun to appreciate the subtle differences and advantages that nickel can offer as a catalyst compared to palladium. Whereas palladium catalysis typically cycles in even, two-electron manifolds Pd(0)/Pd(II) and Pd(II)/Pd(IV), the corresponding nickel(I) and (III) oxidation states are more easily accessed, opening a plethora of catalytic opportunities. Notably, nickel catalysts have found widespread application in tandem with stoichiometric organometallic reagents allowing reactivity manifolds such as asymmetric cross coupling of alkyl-electrophiles to be realised.[3] A comprehensive review of recent developments in homogeneous nickel catalysis provides an excellent overview of the field as a whole, covering a range of sub-disciplines.[4] One such branch is the intensive area of research that has developed around the concept of nickel-catalysis that can be activated or 'switched-on' by the addition of stoichiometric metallic reducing agents, particularly zinc or manganese. More specifically, recent excellent review articles have been published that focus on catalysis, including nickel catalysis, in the context of reductive electrophile-electrophile cross coupling[5] and reductive couplings employing carbonyl-type compounds.[6] Although reactions falling into both these categories are discussed in this perspective, the aforementioned articles provide more comprehensive overviews of these specific transformations and are highly recommended reading. Rather, with this present article, our aim is to demonstrate the diversity and breadth of transformations made possible by reductive nickel catalysis in the presence of stoichiometric metallic reducing agents, with specific attention devoted to mechanistic studies into such catalytic systems. Indeed, it is through such mechanistic understanding that remarkable recent progress has been made via the productive merger of nickel- and photoredox-catalysis[7]. Sadly discussion of such chemistries is outside the scope of this short-review and constitutes a large, emerging field of catalysis requiring its own stand-alone summarisation.[8] Likewise, the discussion of C-H activation and cross-coupling reactions that typically require Ni(0) catalysts from the outset of the reaction are also outside the scope of this article, but are adequately summarised in existing review articles (Scheme 1 – *Right*).[9]

Instead, focus will be given to synthetic methods that employ stable Ni(II) salts as catalyst precursors that are reduced *in situ* to the active catalytic species by stoichiometric metallic reducing agents (Scheme 1 – *Left*). In order to devote the requisite amount of attention to such transformations, we have elected to focus on recent advances in the field, particularly in the past five years (2012 onwards). Nevertheless, to provide context to the development of the transformations described herein, seminal examples have been highlighted and discussed where appropriate.



Scheme 1 This review focuses on nickel catalysis from Ni(II) precatalysts enabled by stoichiometric metallic reducing agents and does not include Ni(0) catalysis, nickel catalysis with organometallic reagents, or nickel/photoredox dual catalytic systems.

2. Nickel Catalysis Enabled by Metallic Reducing Agents

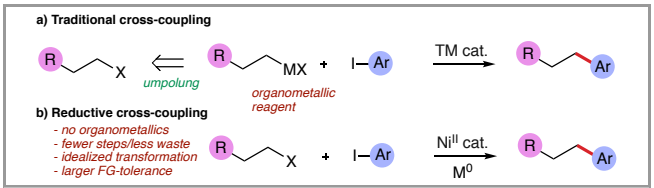
The formally reductive dimerisation of electrophiles, such as alkyl halides, in the presence of metals is amongst the oldest reaction classes of organometallic chemistry.[10] Nevertheless, truly catalytic methods that seek to implement such a reductive strategy in a controllable, useful manner have only recently emerged from the synthesis community. One of the earliest general reactions of this type is the Nozaki-Hiyama-Kishi reaction, the addition of allyl or vinyl halide to an aldehyde.[11] Although a reaction with a complicated history of mechanistic elucidation,[12] modern versions rely upon co-nickel and chromium catalysis with overall catalytic turnover mediated by stoichiometric manganese(0).[13] Fundamentally the success of reductive nickel catalysis depends upon the synergistic interaction of all catalytic components. Fine-tuning of the catalyst/ligand architecture in combination with different reducing agents is required with each different electrophile combination in order to minimise undesired off-cycle reactivity and ensure efficient catalyst turnover. Table 1 lists redox potentials relevant to the chemistry described in this review article.[14] The general trend suggests that in each class of reagents, the corresponding iodide is more easily reduced than the bromide, which in turn is more easily reduced than the chloride. Arylhalides have the most negative redox potential and are thus the most difficult electrophilic species to reduce. The corresponding alkyl halides are more facile to reduce to their alkyl radical counterparts and the benzylhalides are slightly more easily reduced owing to the stabilisation afforded to the nascent benzylic radical. Comparison of the two electron reduction potentials of Zn^{2+}/Zn^0 and Mn^{2+}/Mn^0 shows that of the commonly employed reducing agents, manganese is the more powerful of the two. The listed reduction potentials cannot be taken as an absolute prediction for the success of *de novo* reactions, but offer a rough guide as to the feasibility of elementary steps in the reactions described herein and are worth considering when contemplating the mechanistic scenarios described in the following pages.

Redox Couple	*E vs SCE [V]*
Ar-Cl/Ar$^{\cdot}$ + Cl$^-$	-2.80 — -2.10
Ar-Br/Ar$^{\cdot}$ + Br$^-$	-2.65 — -1.79
Ar-I/Ar$^{\cdot}$ + I$^-$	-2.15 — -1.20
$CH_3CH_2Cl/CH_3CH_2^{\cdot}$ + Cl$^-$	-1.13
$CH_3CH_2Br/CH_3CH_2^{\cdot}$ + Br$^-$	-0.88
$CH_3CH_2I/CH_3CH_2^{\cdot}$ + I$^-$	-0.80
$PhCH_2Cl/PhCH_2^{\cdot}$ + Cl$^-$	-0.67
$PhCH_2Br/PhCH_2^{\cdot}$ + Br$^-$	-0.39
$PhCH_2I/PhCH_2^{\cdot}$ + I$^-$	-0.38
$[Ni(bpy)_3]^{2+}/[Ni(bpy)_3]^{+}$	-1.24
Mn^{2+}/Mn^0	-1.44
Zn^{2+}/Zn^0	-1.02

Table 1 A selection of relevant redox potentials.

3. Reductive Cross-Coupling

Traditional cross-coupling reactions unite an electrophilic aryl halide or pseudohalide species with a nucleophilic organometallic reagent. This is also true of nickel-catalysed cross-couplings where significant recent progress has been made in the coupling between activated phenol derivatives and boronic acids.[15] Additionally, the recent advances made in the realm of asymmetric cross-couplings between alkyl electrophiles and organometallic reagents should not be overlooked.[16] Nevertheless, such organometallic reagents are often prepared via metal insertion into the corresponding alkyl or aryl halide, an extra synthetic step that also generates additional waste (Scheme 2a - *Top*). Reductive cross-coupling is a strategy that eliminates this additional 'umpolung' step and instead marries two electrophilic reagents, typically halides, through the interaction of a catalytic species and a stoichiometric reducing agent in order to allow the catalytic cycle to turnover (Scheme 2b - *Bottom*).[5]

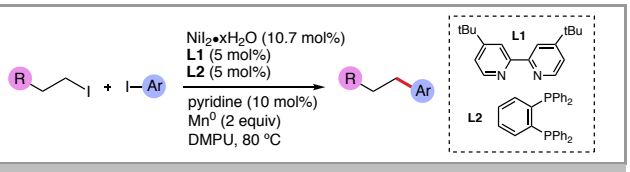


Scheme 2 A schematic overview of a) Traditional cross-coupling reactions in comparison to b) reductive cross-coupling reactions.

The development and implementation of such reductive cross-coupling strategies has been rapid owing to the operational simplicity of the reactions and the potential advantages such a route offers. The removal of highly reactive (often pyrophoric) organometallic reagents means that cryogenic, rigorously anhydrous or anaerobic conditions are no longer required and also offers the possibility of wider functional group tolerance. Over the past five or six years, research into reductive cross-coupling type reactions has been intensive, and important methodological and mechanistic breakthroughs have been made. The following sections summarise this recent progress.

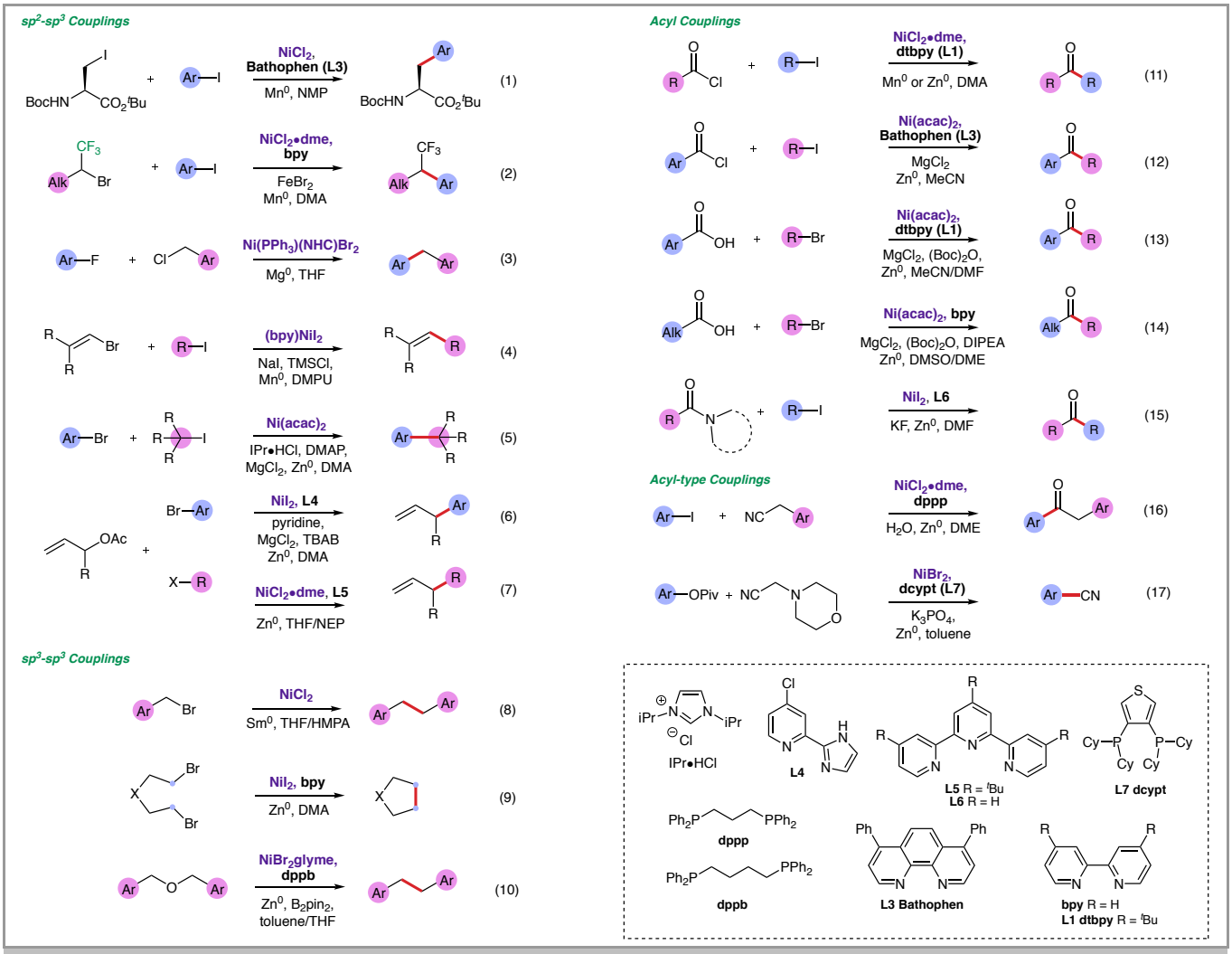
3.1 Alkyl-Aryl Reductive Cross-Couplings

Reductive cross-couplings as a general concept materialised with the seminal 2010 report by the Weix laboratory disclosing the selective cross-coupling between equimolar quantities of alkyl and aryl halide (Scheme 3).[17] In order to deliver high levels of cross-selectivity, both a bipyridyl and a phosphine ligand were required and pyridine was included as an additive to supress ß-hydride elimination in the alkyl species.



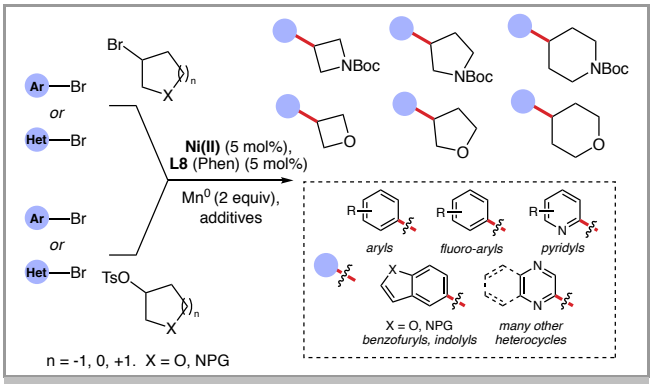
Scheme 3 Reductive cross-coupling of alkyl- and aryl iodides; a report that revitalised interest in the field of reductive coupling.

This combination of catalysts, ligands and additives delivered the cross-coupled products in high yields and with refinement; the union between aryl and alkyl bromides was also disclosed.[18] These initial advances kick-started the development of related reductive coupling systems from other research groups around the globe. A specific methodology for the reductive cross-coupling of amino acids was developed by Liu and co-workers with no observed erosion of stereointegrity (Scheme 4, entry 1).[19] A similar reductive cross-coupling strategy was reported for the union of α-trifluoromethylated secondary aliphatic bromides and aryl iodides leading to the corresponding products in excellent yields (Scheme 4, entry 2).[20] Catalytic conditions for the reductive cross-coupling of aryl-fluorides and benzylic chlorides have also been reported, leading to the formation of diarylmethane species (Scheme 4, entry 3).[21] In addition to aryl halides, nickel-catalysed reductive conditions have been developed for the cross-coupling of vinyl bromides with a variety of alkyl halides (Scheme 4, entry 4).[22] Additionally, the stereospecific formation of aryl and heteroaryl indanes was reported by Jarvo and co-workers. The nickel-catalysed intramolecular cyclisation between an aryl-bromide and a secondary benzylic pivalate was found to proceed with near complete retention of stereochemistry.[23] Given the prevalence of saturated and unsaturated heterocyclic motifs in drug-like molecules and agrochemicals, there is significant interest in engaging them in reductive cross-coupling reactions. With this in mind, the Molander group has reported conditions that enable the reductive-coupling of (hetero)aryl bromides with secondary aliphatic halides[24] and tosylates.[25]



Scheme 4 Overview of nickel-catalysed reductive cross-coupling reactions.

The catalytic combination of nickel(II) complex, ligand and stoichiometric manganese, conditions optimised through high-throughput experimentation, allows access to a range of pharmacophore-like structures containing numerous saturated heterocyclic motifs in combination with heteroaromatic cores (Scheme 5). Similar reaction conditions were also applied to the preparation of substituted borazaronaphthalenes; potentially interesting compounds for material science applications.[26]



Scheme 5 Overview of the reductive cross-coupling methodologies developed by the Molander laboratory. Such methods are specifically targeted at generating pharmaceutically-interesting heterocycle-bearing building blocks. Phen = 1,10-phenanthroline.

The examples detailed so far typically engage aryl halides in reaction with primary or secondary alkyl halides. Tertiary alkyl halides have proven significantly more difficult to control in such reductive coupling reactions owing to their propensity to undergo ß-hydride elimination before engaging in cross-coupling-type reactivity. Nevertheless, in 2015 a protocol was developed by the group of Gong, allowing such tertiary substrates to be engaged in reductive couplings with aryl bromides. Key to the success of this system is a pyridine or DMAP additive in combination with a diazolium salt which in tandem supress ß-hydride elimination and boost the reaction efficiency (Scheme 4, entry 5).[27] The Weix and Gong groups independently developed methodologies that engage allylic acetates in reductive coupling with alkyl and aryl halides respectively (Scheme 4, entries 6 and 7).[28] In addition, a series of reports extends this concept to the reductive conjugate addition of electrophiles to enones, with the resulting enol trapped as the silyl enol ether.[29]

3.2 Alkyl-Alkyl Reductive Cross-Couplings

The success of reaction systems that unite alkyl- and aryl-fragments is dependent on the differing reactivity profiles of the sp^2-reaction partner and the sp^3-reaction partner, and simplistically the differing modes of oxidative addition that these species undergo. In reality, the mechanistic pathway is slightly more nuanced (See Section 3.4), yet the end result is the same – the aryl and alkyl reaction components arrive at union via a polar and radical pathway, respectively, which leads to the high-degree of cross-coupling in such reactions when catalysed by nickel. While such a scenario is clearly advantageous in sp^2-sp^3 cross-couplings, conversely the development of controllable cross-coupling between two sp^2-reaction partners or two sp^3-reaction partners is made significantly more challenging. Consequently, limited progress has been made in reductive sp^3-sp^3 coupling. Nevertheless, Gong and co-workers developed an early, moderately selective $Ni(cod)_2$-catalysed cross-alkyl reductive coupling enabled by zinc,[30] as well as a variant employing B_2pin_2 as the stoichiometric reductant[31] Three recent reports summarise alternative strategies towards such a transformation. The first, reported by the group of Liu, is an intermolecular dimerisation of benzylic bromides (Scheme 4, entry 8),[32] a strategy similar in nature to Weix's 2010 report.[33] The second is the intramolecular reductive cyclisation of aliphatic bromides developed by Gong and co-workers[34] (Scheme 4, entry 9), although it is only applicable in intramolecular scenarios. The third and most recent strategy, developed by Shi, is the deoxygenative coupling of bis-benzylic ethers (Scheme 4, entry 10).[35] Relying upon a nickel-bisphosphine catalyst system in the presence of zinc(0) and B_2pin_2, this report primarily details the deoxygenative coupling of symmetrical naphthyl-derived ethers. However, it offers promising initial results that hint at the possibility of developing selective sp^3-sp^3 reductive cross-coupling reactions.

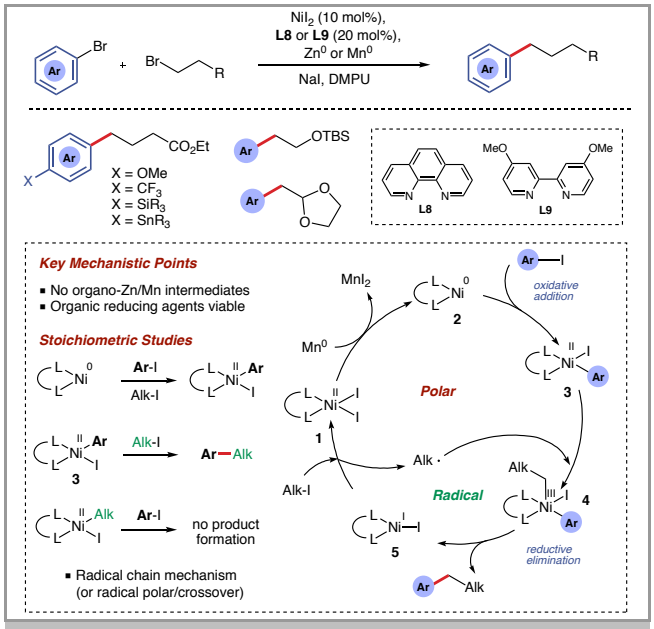
3.3 Acyl Reductive Cross-Couplings

Alongside alkyl-aryl and alkyl-alkyl coupling systems, much attention has been devoted to the development of corresponding acyl coupling reactions. Weix and Gong independently reported catalytic systems for the coupling of acid chlorides with alkyl chlorides (Scheme 4; entries 11 and 12),[36] a reaction-type later extended to the 'one-pot' coupling of benzoic acids with alkyl bromides via the intermediacy of reactive anhydrides (Scheme 4, entry 13).[37] The same catalytic system was then refined to enable the reductive coupling of alkyl carboxylic acids with tertiary alkyl and glycosyl halides, yielding a variety of dialkyl ketones in an efficient process (Scheme 4, Entry 14).[38] Similar nickel-catalysed systems have been developed that enable the reductive coupling of alkyl iodides with chloroformates (Scheme 4, entry 15)[39] and with activated amides (Scheme 4, entry 16).[40] Other related transformations include the reductive coupling between aryl iodides and benzylic nitriles which upon hydrolysis yield aryl(benzyl)ketones[41] (Scheme 4, entry 17), and the direct cyanation of aryl pivalates (Scheme 4, entry 18).[42]

3.4 Mechanistic Understanding of Reductive Cross-coupling Reactions

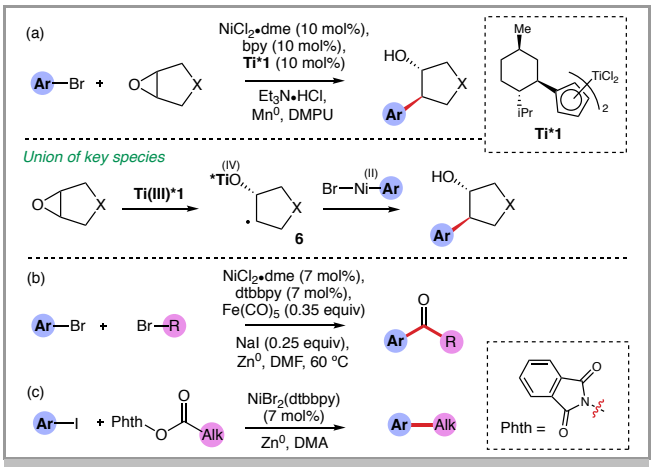
Mechanistic studies into reductive cross-coupling reactions point towards a radical chain mechanism or polar/radical crossover mechanism.[43] Importantly, it has conclusively been demonstrated in many studies that the Zn(0) or Mn(0) can be replaced with organic reducing agents such as TDAE without the reactions suffering a severe drop in efficiency. This effectively rules out organozinc or organomanganese intermediates in such reductive coupling reactions. Instead, the accumulation of mechanistic studies leads to the following conclusions and proposed mechanism. The *in situ* formed nickel(II) bipyridyl complex **1** is reduced to nickel(0) species **2** which reacts selectively with aryl halides to form arylnickel(II) complex **3** (Scheme 6). Stoichiometric studies have shown that this complex reacts with alkyl halides in the absence of additional reducing agent to form the alkyl-aryl cross-coupled product. In contrast, alkyl nickel complexes do not react with

aryl halides under typical reaction conditions. Racemisation and cyclopropyl-substrate studies are highly suggestive of a carbon-based radical intermediate, whereas a radical clock study[44] at varying nickel concentrations is consistent with the proposed radical chain mechanism with radical formation and consumption taking place at differing nickel centres. Taken together, this evidence suggests a cross-over mechanism whereby arylnickel(II) intermediate **3** reacts with the generated alkyl radical to form nickel(III) intermediate **4** which, after reductive elimination, gives the cross-coupled product. Halide abstraction by Ni(I) intermediate **5** then allows the alkyl radical to enter the catalytic cycle and in turn generates Ni(II)X_2 **1**, which re-enters the cycle via reduction to Ni(0). Additional studies suggest that arylnickel(II) intermediate **3** is the resting state of the system, a scenario that explains why its concentration must remain in excess compared to the highly reactive alkyl radical in order to avoid side-reactions. This mechanistic scenario elegantly explains the experimental results and high levels of cross-coupling compared to homo-coupling of either electrophile. The key feature of the catalytic cycle is the self-regulatory system that minimises the amount of alkyl radical relative to crucial arylnickel(II) intermediate **3**. In effect, the turnover of the system amounts to a steady-state or slow release of each reactive component and thus engenders high levels of selectivity for the union between arylnickel(II) and alkyl radical. Although the mechanistic scenario above focuses on the coupling of aryl-halides, complementary mechanistic studies into the related coupling of acyl-halides have delineated an almost identical, radical-chain mechanistic pathway.[45] Ren, Zhang and Gong have also recently disclosed the reductive coupling of aryl- and vinylhalides. DFT studies provide support for a mechanistic pathway that proceeds via the key union of a nickel(I) vinyl species with an arylhalide to give a nickel(III) intermediate, a scenario congruent with prior mechanistic work albeit in an sp^2-sp^2 coupling manifold.[46]



Scheme 6 Mechanistic investigations have revealed a radical chain reaction mechanism that combines both polar and radical elementary steps.

With enhanced mechanistic understanding came the realisation that reductive couplings were not limited to the incorporation of radicals generated from electrophiles, but that radicals introduced into the catalytic cycle via alternative, and even co-catalysed, pathways could serve as competent coupling partners (Scheme 7). An excellent demonstration of this insight was the merger of nickel and titanium catalysis in the enantioselective arylative ring opening of meso-epoxides.[47] Chiral titanocene catalyst **Ti*1** is proposed to generate a stereodefined transient ß-titanoxy radical **6** from the epoxide, which is captured by the corresponding arylnickel(II) species. Reductive elimination forges the new carbon-carbon bond, whilst reduction of both catalysts closes the catalytic cycle (Scheme 7a).

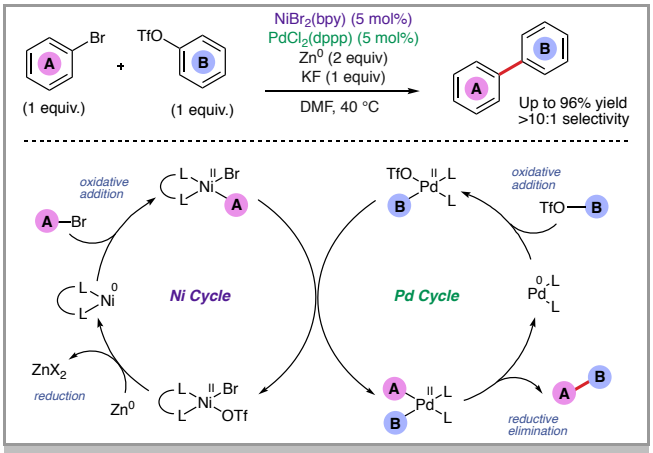


Scheme 7 Follow-up systems developed through mechanistic understanding; a) enantioselective epoxide ring-opening, b) carbonylative ketone preparation, c) decarboxylative reductive cross-coupling.

Additionally, as both the cross-coupling of aryl and acyl halides operate via the same mechanistic pathway, improved methodologies seeking to take advantage of this mechanistic convergence were developed. The nickel catalysed carbonylative cross-coupling between aryl and alkyl halides using $Fe(CO)_5$ as a CO source was reported in 2014[48] as an improvement to related existing methods[49] (Scheme 7b). An alternative means by which to engage alkyl radicals in reductive cross-couplings via the decarboxylative fragmentation of activated esters was also devised (Scheme 7c).[50]

Despite significant advances in nickel-catalysed cross-couplings, one challenge that has remained elusive is the intermolecular hetero-cross coupling of substrates at the same oxidation level (sp^3-sp^3 or sp^2-sp^2), where existing strategies have typically relied upon electronically biased substrates.[51] To address this issue, the Weix laboratory has very recently developed a dual nickel and palladium catalysed selective cross-coupling that does not rely on electronically biased substrates. Key to this protocol is the differing reactivities and thus the complementarity of the two transition metal catalysts. The aryl bromide undergoes selective oxidative addition with the nickel-bpy catalyst, whilst the aryl triflate interacts exclusively with the palladium catalyst. Transmetallation delivers the second aryl group to palladium, whilst the triflate is transferred to nickel. Reductive elimination from palladium

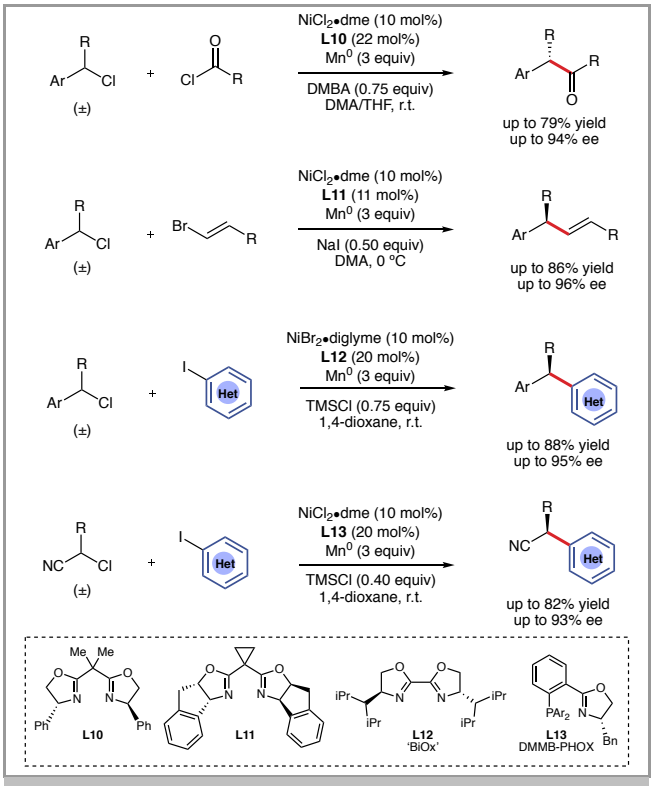
generates the cross-coupled bis-aryl product and regenerates Pd(0). Zinc(0) acts as the terminal reductant for the catalytic cycle, reducing nickel(II) back to nickel(0) (Scheme 8). The authors propose a similar mechanistic rationale as in their previous studies to account for the excellent hetero-coupling selectivity. Namely, that it is the productive interaction of a persistent intermediate (Pd^{II}(Ar)OTf) with a transient, highly reactive species (Ni^{II}(Ar)Br) that results in a rapid transmetallation, allowing synchronisation and self-regulation of the two catalytic cycles.



Scheme 8 Dual nickel and palladium catalysed reductive cross-coupling of electronically unbiased arenes.

3.5 Enantioselective Reductive Cross-Coupling Reactions

In tandem with developments in reductive cross-coupling methodologies, much attention has been focused toward the development of catalytic asymmetric protocols. Given that the vast majority of the previously described approaches employed bipyridyl-type ligands, it follows that the use of chiral bisoxazoline-derived ligands would be able to render such processes enantioselective. Beginning in 2013, the Reisman group disclosed the enantioselective cross-coupling of racemic secondary benzylic chlorides with acyl-chlorides (Scheme 9, entry 1). The combination of a nickel precatalyst with C2-symmetric bis-oxazoline ligand **L10** in the presence of manganese and 2,6-dimethoxybenzoic acid generated the desired ketones bearing an α-stereogenic centre in up to 94% ee.[52] The Reisman group further developed this reaction system and one year later reported a related coupling reaction between secondary benzylic chlorides and vinylhalides, once more in excellent levels of enantiomeric excess.[53] Alongside a different additive, NaI, the bis-oxazoline ligand structure was modified (**L11**) in order to optimize enantioselectivity (Scheme 9, entry 2). This report was followed once more by the successful extension to the enantioselective, reductive cross-coupling of secondary benzylic halides with aryl iodides, a reaction for which a new BiOx ligand **L12** was found to be optimal (Scheme 9, entry 3).[54] In a related transformation, the same group also reported the enantioselective, reductive cross-coupling of racemic, secondary α-chloronitriles under almost identical reaction conditions.[55] Curiously however, a phosphinooxazoline ligand **L13** was found to be optimal in this transformation (Scheme 9, entry 4). The mechanistic profile and mode of enantioinduction in such reactions is yet to be fully elucidated, however control experiments by the authors are in line with the aforementioned mechanistic studies. The mechanistic origin of enantioinduction may be envisaged to arrive through stereoconvergent oxidative addition or via a reductive elimination-mediated dynamic kinetic resolution-type mechanism. The authors comment that: "(It is) unclear whether absolute stereochemistry is set in the oxidative addition or reductive elimination steps."[52] However, the authors also suggest that mechanistic investigations are currently ongoing.



Scheme 9 Catalytic, enantioselective reductive cross-coupling reactions developed by Reisman and co-workers.

3.6 Reductive Cross-Coupling Conclusions

The previous section highlights the significant recent advances in this area and demonstrates that reductive cross-couplings catalysed by nickel can be considered workhorse reactions, particularly those between sp^3 and sp^2 centres. Such combinations of reactants are ideally suited to the partitioning radical chain mechanism that amplifies productive cross-coupling in such reaction manifolds. In-depth mechanistic studies have proven indispensable to the understanding of such catalytic processes and consequently to the development of current state of the art catalytic systems, including those that merge nickel-catalysis and photoredox catalysis. Further unexpected advances in this burgeoning field will doubtlessly be inspired by deeper mechanistic understanding.

Significant progress has also been made in the development of catalytic, enantioselective cross-coupling reactions, yet the scope of such transformations is presently limited to more tractable benzylic-type reaction partners. Further forays into this field will no doubt seek to engage less-activated alkyl substrates in enantioselective coupling reactions. Enhanced understanding of ligand-design can be envisaged as a means by which to improve such methodologies, moving towards more

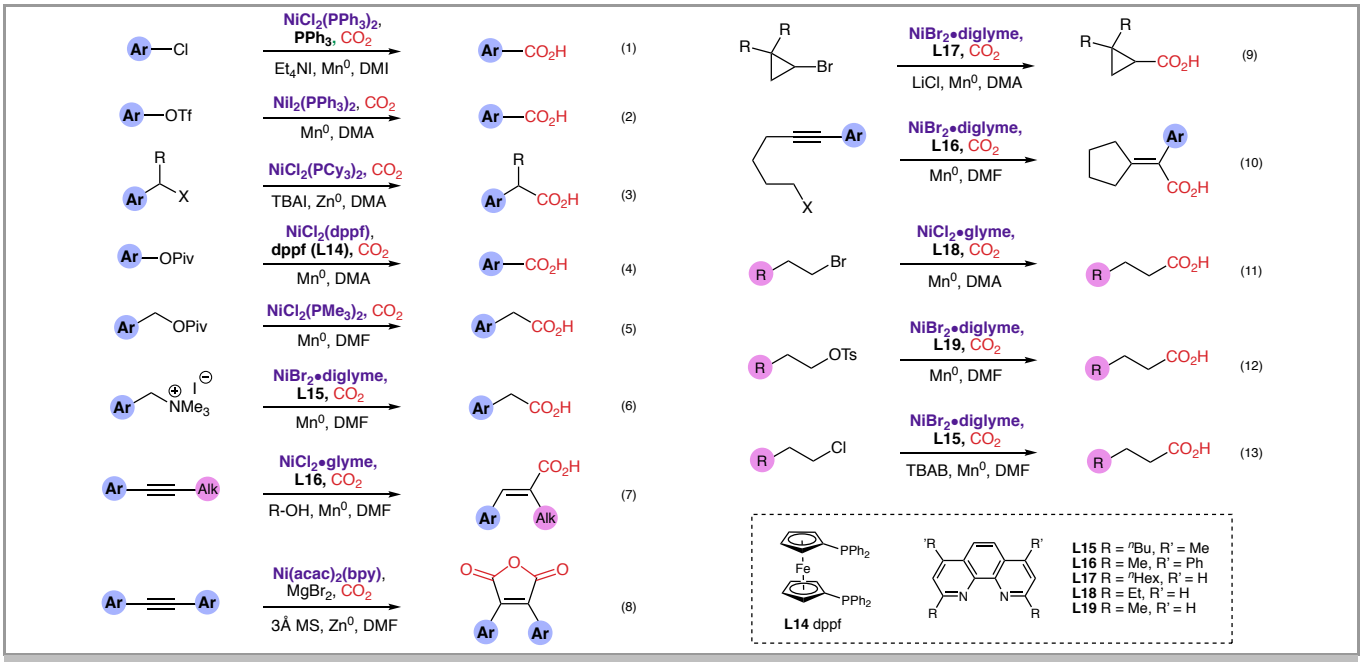
active and more sustainable catalytic systems. Indeed, high-throughput techniques are already revealing ligand architectures that enable the reductive cross-coupling of previously unreactive substrate classes.[56]

4. Reductive Carboxylation and Acylation-type Reactions

The chemical community is already acutely aware of the need to develop synthetic methodologies that make use of carbon dioxide as a C1-carbon source given the negative environmental impacts of increasing atmospheric CO_2 levels. In fact, carbon dioxide is an ideal reagent; it is relatively non-toxic and to all intents and purposes is infinitely abundant. A challenge to the use of carbon dioxide is its high kinetic and thermodynamic stability, imparting a somewhat recalcitrant reactivity profile. Nevertheless, the synthetic community has set out to develop methodologies, particularly those based upon transition-metal catalysis, that seek to overcome this lethargy. The use of highly reactive organometallic reagents including organolithiums, Grignard reagents, organozincs and stannanes offers reliable, if not economical or sustainable, reactivity.[57] Seminal work by Osaka and Yamamoto suggested, at least stoichiometrically, that nickel salts were able to activate carbon dioxide[58] while mechanistic studies by Jutand and co-workers also gave insight into the redox feasibility of such transformations[59] and suggested that homogeneous fully catalytic methodologies were in fact viable.

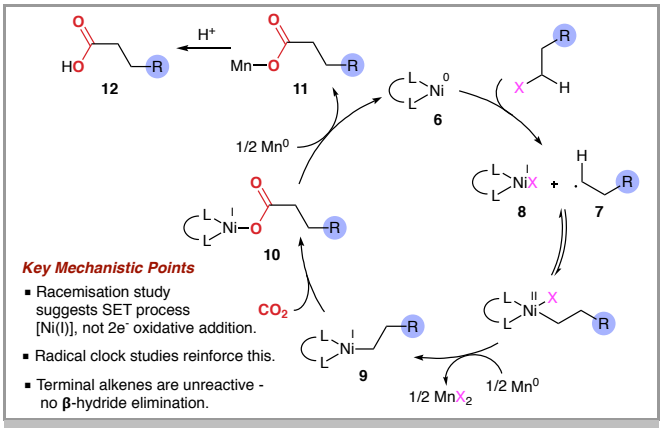
4.1 Reductive Carboxylation

No doubt drawing inspiration from Martin's seminal 2009 report on the reductive (Pd/Et_2Zn) carboxylation of aryl bromides,[60] a significant breakthrough in rendering carboxylation processes sustainable was made by the Tsuji laboratory in 2012. A catalytic protocol employing a nickel phosphine complex in the presence of superstoichiometric manganese allowed for the efficient carboxylation of aryl-halides (Scheme 10 - entry 1).[61] Importantly, this reaction operates at room temperature and with just 1 atm of carbon dioxide. This initial conceptual breakthrough has spurred rapid advances in this field, with a myriad of substrates now able to be carboxylated under 'reductive-nickel' catalysis conditions. The remarkable recent progress is summarised in Scheme 10.[6] The Tsuji group extended their initial protocol to allow the use of aryl and vinyl triflates (Scheme 10, entry 2),[62] whilst the Martin laboratory began to explore alternative aryl- and benzyl- pseudo-electrophiles. In doing so, they developed catalytic systems for the carboxylation of benzylic halides (Scheme 10, entry 3),[63] aryl and benzyl pivalates (Scheme 10, entries 4 and 5),[64] and benzylic ammonium salts (Scheme 10, entry 6).[65] While all these reactions systems are similar in requiring a nickel salt, reducing agent and polar amide solvent, each different substrate class required the use of a slightly different ligand structure for carboxylation to occur in high yields. For benzylic halides and pivalates, mono-dentate phosphine-ligands proved optimal, whilst dppf was more effective for the carboxylation of aryl pivalates. The carboxylation of benzylic ammonium salts however was optimised using phenanthroline-derived ligands. Using similar catalytic strategies, the carboxylation (Scheme 10, entry 7)[66] and double carboxylation (Scheme 10, entry 8)[67] of internal acetylenes was developed alongside the carboxylation of ynamides.[68] In 2015, the Martin laboratory developed a reductive cyclisation/carboxylation of primary and secondary aliphatic bromides bearing distal acetylene units. Nickel-catalysed cyclisation forms 5-membered carbocycles bearing exocyclic, tetrasubstituted carboxylated olefins (Scheme 10, entry 10).[69] Similar catalytic conditions were also employed in the direct carboxylation of bromo-cyclopropanes, taking advantage of the sp^2-like character of such ring-systems (Scheme 10, entry 9).[70] Between 2014 and 2016, the Martin group also disclosed a series of reports detailing the nickel-catalysed, direct carboxylation of terminal aliphatic bromides[71], tosylates[71] and finally chlorides;[72] such systems being particularly impressive given the significant progress made in moving to less-activated substrates in such a short



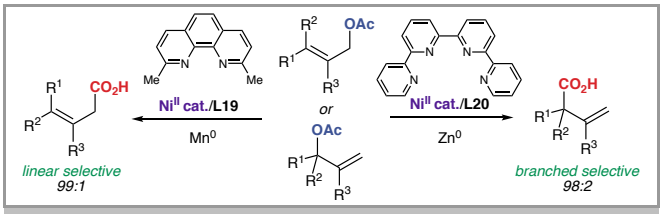
Scheme 10 Overview of nickel-catalysed reductive carboxylation reactions.

time-span (Scheme 10, entries 11, 12 and 13, respectively). The following general mechanistic scenario for such carboxylation reactions can be proposed, even if subtle influences of the ligand in each system remain unclear. The catalytic cycle initiates with reduction of the Ni(II)-complex to Ni(0) **6**, followed by single electron transfer (SET) to the alkyl halide to form the transient alkyl radical **7** and Ni(I)halide species **8**. Recombination, and subsequent reduction by manganese(0) yields reactive η1-Ni(I)alkyl species **9**, which undergoes CO_2 insertion to yield **10**. Reduction, once more by manganese(0), allows the catalytic cycle to turn over and yields manganese carboxylate **11** which is hydrolysed during the work-up to yield the carboxylic acid **12**. The loss of stereochemical integrity at the halide-bearing carbon during the reaction, and the ring-opening of radical clock substrates, provides evidence for a key single electron transfer step, rather than a classical two-electron oxidative addition. With alkyl halide substrates, the corresponding terminal alkenes are unreactive under the reaction conditions, suggesting that initial β-hydride elimination is not a contributing mechanistic pathway.



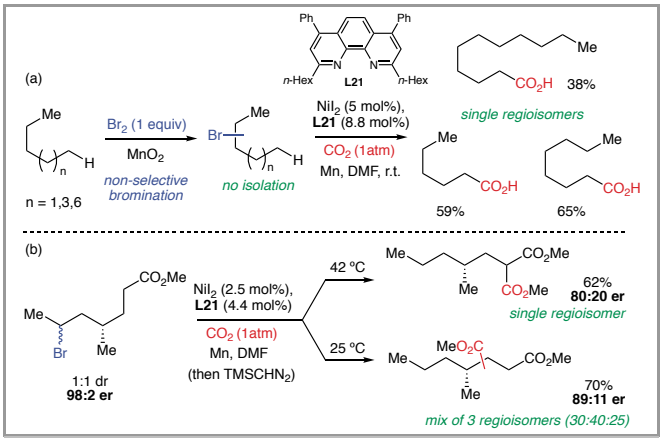
Scheme 11 General mechanistic proposal for nickel-catalysed reductive carboxylation of a variety of halide/pseudohalide substrates.

All the systems detailed in Scheme 10 share significant similarities in that a nickel pre-catalyst, in combination with a stoichiometric reducing agent and a polar amide solvent is required. However, the most salient feature in the aforementioned reactions is the influence of the ligand architecture, in that each different substrate class or reaction system requires tweaking of the ligand structure. The importance of the ligand in such transformations is perhaps most clearly illustrated by the regioselective carboxylation of allylic acetates developed by the Martin laboratory. A protocol was developed whereby highly substituted allylic acetates could be carboxylated in the presence of a nickel-catalyst, stoichiometric reducing agent and 1 atm of carbon dioxide.[73] By judicious selection of ligand, this protocol was rendered highly selective for either the linear carboxylation product, by using neocuproine **L19** as a ligand; or the branched carboxylation product, using a quaterpyridine ligand **L20** (Scheme 11). Moreover, this ligand effect is just as pronounced when either the branched or linear allylic starting material is employed in this transformation. Further research has also developed related protocols for the regioselective carboxylation of allylic alcohols.[74,75] The authors suggest that in-depth mechanistic studies of such systems are in progress, however preliminary studies allow the authors to hypothesise that this regiodivergence is directly attributable to the ligand structure. The authors speculate that the Ni/phenanthroline catalysed carboxylation proceeds via an η1-Ni(I) intermediate with carboxylation occurring at the α-carbon, whilst the Ni(quaterpyridyl) catalysed carboxylation occurs via a slightly different pathway with carboxylation occurring at the γ-carbon. Initial speculations for this selectivity switch could hint at the formation of an η1-Ni(II) intermediate, the possibility that **L20** plays an ancillary role to deliver the CO_2 to the γ-carbon, or that **L20** (and related terpyridines) act as redox-active ligands in such systems.



Scheme 12 Ligand controlled, regioselective carboxylation of allylic acetates.

Investigations into the carboxylation of a variety of substrate classes, alongside advances in ligand design have culminated in the development of a regioconvergent, selective terminal carboxylation of alkyl bromides.[76] Subjecting readily available linear alkanes to a non-selective, oxidative bromination yields a mixture of regioisomeric alkylbromides. A non-purified mixture of these bromides is then subjected to reductive carboxylation conditions with a nickel-catalyst system bearing the bespoke dihexylphenanthroline ligand **L21**. Via a chain-walking type mechanism, carboxylation occurs exclusively at the terminal position of the alkyl chain, resulting in convergence to a single isomer of the alkyl carboxylate (Scheme 13a).



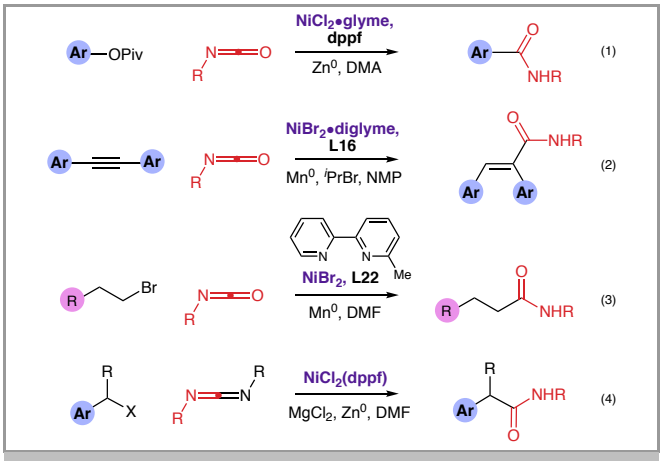
Scheme 13 Regioconvergent terminal carboxylation of regioisomeric mixtures of alkylbromides.

While selective carboxylation at the terminal position can be obtained at room temperature, simple elevation of the reaction temperature leads to the selective formation of the branched carboxylic acid isomer, a selectivity switch demonstrated across a range of substrate classes. The authors conclude this report by demonstrating that an enantioenriched substrate can also be subjected to the carboxylative protocol without significant erosion of enantiointegrity. Under the developed conditions at

42 °C, the alkyl bromide (98:2 er) is selectively carboxylated to yield a single regioisomer of the product (80:20 er) (Scheme 13b). Slightly higher ers were maintained at lower temperature, yet a mixture of regioisomeric carboxylates is obtained. Nevertheless, this demonstration constitutes a rare example where pre-existing stereogenic centres are not eroded via a transition-metal 'chain-walking' mechanistic pathway.

4.2 Reductive Amidation-type Reactions

In addition to employing carbon dioxide as the electrophilic component in such transformations, related systems using isocyanates (Scheme 14, entries 1-3) have been developed, leading directly to amide products. Reductive nickel catalysed systems have been developed for the direct amidation of aryl-pivalates,[77] alkynes[78] and aliphatic bromides.[79] The use of carbodiimides as the electrophilic component, also leading to amide products, (Scheme 14, entry 4) has also been reported under very similar reaction conditions.[80]



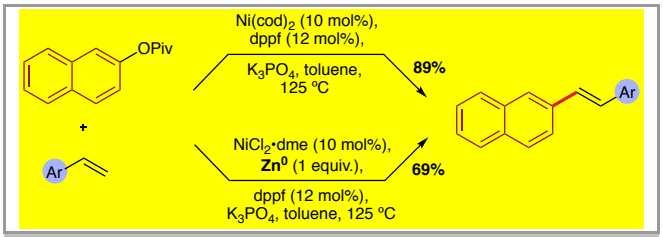
Scheme 14 Nickel-catalysed reductive amidation reactions.

5. Miscellaneous Reactivity

The use of nickel catalysts in tandem with stoichiometric metallic reducing agents have also found application in areas other than in cross-coupling manifolds. These include a less easily categorized array of chemistry which will be summarised in the following section. The nickel-catalysed reductive stannylation of aryl halides was recently reported by Komeyama and co-workers.[81] Variants of the Simmons-Smith cyclopropanation reaction catalysed by nickel are well developed[82] and recent examples have demonstrated the use of low loadings of binuclear nickel species as viable catalysts, offering advantages in both activity and substrate compatibility.[83] A variety of cycloaddition methodologies have been developed that are catalysed by nickel. $Ni(cod)_2$ in tandem with NHC or bisphosphine ligands have proven particularly effective for cycloadditions between alkynes/diynes and a variety of 2π-cycloaddition partners,[84] however corresponding reductive variants of such methodologies are seemingly less developed than their cross-coupling counterparts.

5.1 Heck Reactivity

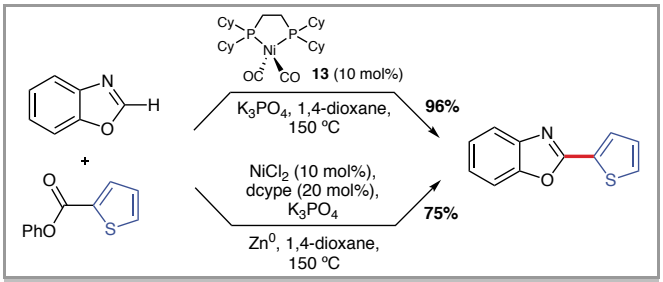
The nickel-catalysed Heck reaction of aryl pivalates was disclosed by Watson and co-workers using a nickel(0) pre-catalyst, dppf and K_3PO_4. Although this methodology was primarily developed using $Ni(cod)_2$ as a pre-catalyst, the ability to substitute for a nickel(II) salt in combination with stoichiometric zinc(0) is also demonstrated with little impact upon the efficacy of the catalytic system (Scheme 15).



Scheme 15 Nickel-catalysed Heck reaction of aryl pivalates. ***Top*** - employing a Ni(0) precatalyst. ***Bottom*** - Pathway B employing a Ni(II) salt in combination with Zn(0).

5.2 C-H Activation

In addition to traditional cross-coupling reactions, nickel catalysts have also proven particularly useful in C-H activation methodologies.[9] Nevertheless, the majority of nickel-catalysed C-H activation systems typically fall under the umbrella of directed C-H activation, whereby a redox-active,[85] typically quinoline-derived directed group allows nickel(II) salts to engage directly in the catalytic cycle. Non-directed C-H activations on the other hand, typically employ unstable Ni(0) complexes directly, limiting potential uptake of such methods. In 2012, the group of Itami developed the C-H activation/decarboxylative cross-coupling of various heterocycles using nickel(0) catalyst **13**. The authors demonstrated that the same catalytic cycle could be accessed when employing $NiCl_2$ in tandem with superstoichiometric Zn(0) in only slightly diminished yield (Scheme 16).[86]



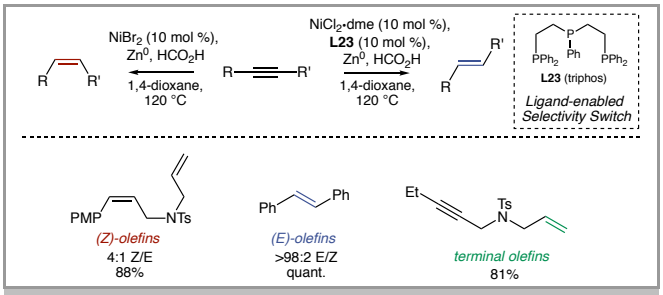
Scheme 16 Nickel-catalysed C-H activation/cross-coupling. ***Top*** - employing Ni(0) precatalyst **13**. ***Bottom*** - employing a Ni(II) salt in combination with Zn(0).

5.3 Reductions & Isomerisations

In 1990, Kudo and Nose reported the reduction of a variety of organic compounds using a stoichiometric $NiCl_2$ and Zn(0) system.[87] The reactions all proceeded in MeOH and typically between 1-6 equivalents of nickel salt were required, in conjunction with 6-12 equivalents of Zn(0). The developed system proved applicable to the reduction of ketones to alcohols, olefins to alkanes, nitriles to amines, nitro-arenes to anilines, and the partial reduction of certain aromatic

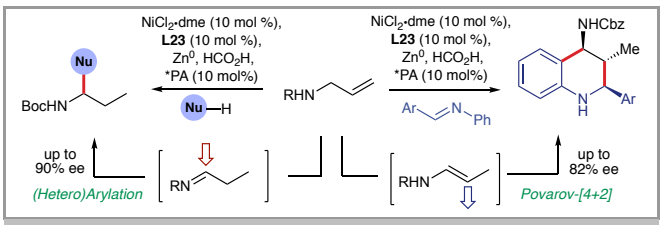
heterocycles. Despite the development of such a simple and widely applicable system, relatively few follow-up studies have aimed to develop catalytic variants of such protocols.[88] However, the use of nickel nanoparticles as catalysts in reductive transformations has become an active field of research.[89]

In 2015, Richmond and Moran reported a nickel-catalysed alkyne semi-reduction methodology leading to the corresponding olefins. The action of a nickel-catalyst in tandem with stoichiometric Zn(0) and HCO_2H as a terminal reductant leads to a highly selective semi-reduction to the (*Z*)-olefin isomer (Scheme 17).[90] The addition of **L23**, triphos, to the catalytic conditions renders the semi-reduction fully selective for the (*E*)-olefin isomer. Mechanistic studies suggest that this ligand-enabled selectivity switch occurs due to the formation of a nickel(triphos) complex, which, in the presence of zinc, acts as a highly active isomerisation catalyst, rapidly converting the initially formed (*Z*)-olefin isomer to the thermodynamically favoured (*E*)-isomer under the reaction conditions. A similar ligand-selective alkyne semi-reduction was also developed the following year using cobalt catalysis where a similar (*Z*)-to(*E*)-isomerisation rationale is invoked.[91] In addition to being effective at geometric isomerisation, this nickel(triphos) catalyst system proved capable for positional isomerisation of allylbenzenes and particularly *N*-allylcarbamates. This isomerisation reactivity was exploited to develop a dual nickel/phosphoric acid catalysed enantioselective functionalisation of *N*-allyl carbamates.[92]



Scheme 17 (*E*)/(*Z*)-Selective nickel-catalysed alkyne semi-reduction.

Isomerisation of the *N*-allylcarbamate yielded an intermediate ene-carbamate, which via judicious selection of reaction partner, could be engaged in either enantioselective α-arylation or in enantioselective [4+2]-cycloaddition (Scheme 18). This report represents a rare example of the productive merger of nickel and organocatalysis.

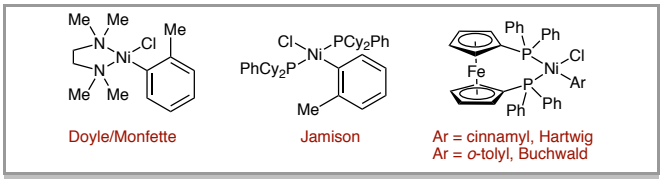


Scheme 18 Enantioselective and Regiodivergent Functionalisation of *N*-Allylcarbamates by Mechanistically Divergent Multicatalysis. *PA = chiral phosphoric acid.

6. Perspectives and Future Directions

At the turn of the last millennium, transition-metal catalysis enabled by stoichiometric metallic reducing agents was not codified, and existing reports of reductive couplings were largely isolated examples, the importance of which went unrecognised for some time. After the palladium 'boom' of the 1980s and 1990s, interest in more sustainable base-metal catalysis has intensified and the field of nickel-catalysis has once more risen to prominence. Alongside significant strides in cross-coupling and reductive coupling methods enabled by Ni(0) catalysts, catalysis by in-situ generated (presumed) nickel (0) intermediates has also proven a fertile area of research. As detailed in the previous sections, stoichiometric metallic reducing agents such as manganese and zinc have proven excellent reduction partners in such transformations, however research teams have begun to explore other means of generating reactive nickel intermediates. Greater mechanistic understanding of the redox-nature of such transformations has also led to the productive merger of nickel and photoredox catalysis, enabling the development of hitherto unrealised transformations.

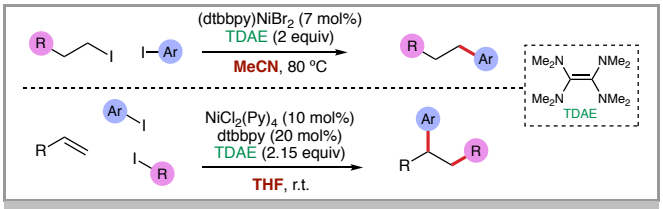
Whilst stable nickel(II) salts such as $NiCl_2$•dme or $NiBr_2$•glyme are more convenient for the operator, the corresponding $Ni(cod)_2$ catalyst is often-times considerably more active, operating at lower temperatures and/or requiring no in situ activation. To this end, a number of research groups have sought to marry the bench-stability of Ni(II) salts with the activity of Ni(0) catalysts. Several successful aryl-nickel precatalysts have been developed bearing bis-amine,[93] mono-dentate[94] or bidentate phosphine ligands (Scheme 19).[95] These precatalysts have been used to great effect in the development of novel nickel-catalysed transformations and systematic study of such catalysts has demonstrated long-term bench stability combined with generally superior catalytic activity to simple NiX_2 salts.[93]



Scheme 19 Air stable arylnickel(II)-pre-catalysts.

A significant drawback of reductive nickel-catalysed transformations is the necessity for an amide or urea solvent, a requirement that limits potential applications of such methods. Additionally, the requirement for superstoichiometric base metal activator also adds to the waste stream of such reactions; another feature that could stand to be improved. This has been recognised by the community, and research aimed at rendering such methodologies more sustainable is already underway, with several notable systems employing B_2pin_2 as terminal reductant already developed (See Section 3). In 2016, the Weix laboratory reported an updated method for the nickel catalysed reductive sp^2-sp^3 coupling in acetonitrile (Scheme 20 – *Top*).[96] Importantly, in addition to a more benign reaction solvent, tetrakis(dimethylamino)ethylene (TDAE), a fully organic reducing agent was employed in this reaction system. The authors propose no perturbation to the reaction mechanism they determined previously and the TDAE acts as a direct

organic replacement for the base-metal reductant. TDAE was also successfully employed by the group of Nevado in the three-component reductive coupling of alkenes to aryl- and alkylhalides.[97] The combination of an unusual nickel precatalyst in tandem with dtbbpy and TDAE in THF enables the 1,2-difunctionalisation of alkenes in a regioselective manner (Scheme 20 – *Bottom*). The authors propose a polar/radical chain reaction mechanism where the crucial nickel-forged C-C bond construction occurs at a nickel(III)aryl/alkyl intermediate accessed via the merger of alkylradical and Ni(II)Ar intermediate.

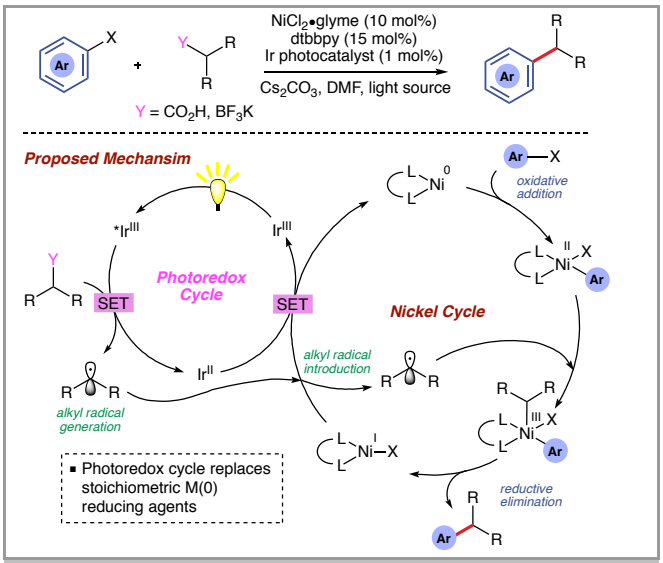


Scheme 20 Development of nickel-catalysed reductive cross-coupling reactions using an organic reducing agent; TDAE in non-amide solvents.

By structural variation and optimisation of the organic reducing agent, a scenario can be envisaged whereby bespoke reducing agents that are completely tuneable can be employed for each different reaction class. In addition, it appears that the use of such organic reducing agents allows reactions to operate outside of amide-based solvents, and so significant sustainability advances can be expected in the near-future of reductive catalysis.

The recent advent of photoredox catalysis, specifically in application to organic transformations has had a transformative impact on the field of homogeneous catalysis.[7] Armed with the mechanistic knowledge of reductive nickel catalysed cross-coupling reactions, research groups have sought to obviate stoichiometric metallic reducing agents and instead turnover such catalytic systems through synchronisation with photoredox cycles (Scheme 21). Remarkable advances have been made, developing from decarboxylative cross-coupling reactions[98] and coupling reactions employing trifluoroborate salts,[99] to a burgeoning field of dual-catalysis enabling numerous reaction-types. Undoubtedly, advances in catalytic systems enabled by the merger of nickel and photoredox catalysis will continue and thus open new vistas in homogenous multicatalysis. Alongside developments with ruthenium and iridium photocatalysts, the wider implementation of photoactive organic dyes can be envisaged.

Organic chemical reducing agents and photochemically generated reductants offer two alternative means by which to turnover reductive catalytic cycles. Electrochemical methods provide a third alternative means that may find wider application, and may particularly find application in larger-scale development and application of such chemistries. A seminal series of reports from Durandetti, Périchon and co-workers has demonstrated both the feasibility and potential practical simplicities of electrochemistry in reductive couplings catalysed by nickel.[100] Indeed, electrochemical variants of many of the reaction systems discussed in this article have already been developed.



Scheme 21 The union of nickel and photoredox catalytic systems.

Additionally, recent investigations in the Baran laboratory have developed an electrochemically enabled, nickel-catalyzed Buchwald-Harwtig-type amination reaction suitable for a range of aromatic and heteroaromatic substrates.[101] The authors establish the feasibility of the system on decagram scale and demonstrate that the reaction does not proceed when the electrical current is removed. The recent announcement of a benchtop electrochemistry setup[102] will provide further impetus to the application of electrochemically-enabled catalysis, and specifically the electrochemical reimagining and improvement of the catalytic systems described herein.

The simplicity of the catalytic systems detailed herein; the relative abundance of nickel(II) salts, combined with often simple ligand architectures gives an appealing platform for the development of sustainable methods based on reductive catalysis. Nickel catalysis enabled by stoichiometric metallic reducing agents is now a well-established field of research with continuing developments appearing frequently in the chemical literature. Mechanistic insights were crucial to the rapid advancement of this area, and have allowed for the development of tantalising 'spin-off' fields, the continued advancement of which will no doubt lead to even more remarkable developments and discoveries over the coming years.

Funding Information

This work was supported in part by a LabEx CSC 'Chemistry of Complex Systems' grant and from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement no 639170).

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(102) IKA has recently (August 2017) announced the commercial release of ElectraSyn 2.0, a stirrer-hotplate sized electrochemical setup.

Biosketches

Joseph Moran (left) was born in Montréal, completing his undergraduate studies at the University of Ottawa (Canada) in 2004, and his Ph.D. at the same institution with Prof. André Beauchemin in 2009. After a brief period as a visiting researcher with Prof. John Pezacki at NRC Canada and two years as an NSERC postdoctoral fellow with Prof. Michael Krische at the University of Texas (USA), he joined ISIS-University of Strasbourg (France) as an assistant professor in 2012. His research interests include supramolecular catalysis, catalyst discovery strategies and systems chemistry that mimics metabolism. He received the prestigious ERC Starting Grant in 2015.
Edward Richmond (right) was born in Sheffield and obtained his MChem degree from the University of York (UK). In 2013, he obtained his Ph.D. from the University of St Andrews (UK) under the supervision of Prof. Andrew D. Smith and since then has been based at ISIS-University of Strasbourg (France) undertaking postdoctoral research with Joseph Moran.